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Comparison of the effect of ferrous sulfate and ferrous gluconate on prophylaxis of iron deficiency in toddlers 6-24 months old: A randomized clinical trial

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Abstract:

BACKGROUND: Iron deficiency anemia (IDA) is one of the most common anemias, especially in children 4–23 months. Therefore, prophylaxis is necessary to improve iron status as well as reduce IDA in Toddlers. The aim of this study was to compare the efficacy of daily supplementation with ferrous gluconate (FG) and ferrous sulfate (FS) on iron status in toddlers.

MATERIALS AND METHODS: A total of 120 healthy toddlers were divided randomly into 2 groups at the Amir-Kabir Hospital, Arak, Iran and received FS and FG from March 2020 to December 2020. Iron status was evaluated at baseline and after 6 months of supplementation. The statistical significance of the differences in iron status between FS and FG groups was calculated using Student's *t*-test and the Pearson' s Chi-square test for qualitative variables. SPSS software (version 16, Chicago, IL, USA) was used for statistical analysis.

RESULTS: Comparison of iron status of FS and FG groups toddlers at baseline and after 6 months of supplementation showed that there was a significant difference in hemoglobin (Hb) (10.46 vs. 12.45, $P = 0.001$) and ferritin level (28.08 vs. 59.63, $P = 0.001$).

CONCLUSIONS: Although prophylaxis with FG led to a higher Hb and ferritin levels, our study recommended that both FG and FS supplements were effective for prophylactic use in the prevention of IDA. However, FG was more effective than FS because FG group that received FG supplementation indicated a higher Hb and ferritin levels in comparison to the FS group that received FS supplementation.

Keywords:

Anemia, ferrous gluconate, ferrous sulfate, iron, iron deficiencies, prophylaxis

Introduction

Iron deficiency anemia (IDA) is the most common micronutrient deficiency affecting nearly one-third of the population and is the leading cause of anemia worldwide.[1] The World Health Organization (WHO) estimates that close to 30%–40% of the world's population are anemic and approximately half of them suffer from IDA.[2]

IDA is one of the most common anemias, especially in children 4–23 months[3] and one-third of children with Iron Deficiency (ID) also have anemia.[4] ID and IDA remain a global concern. Iron is the

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most common nutritional deficiency among children in developing countries. In industrialized countries, despite a significant reduction in the prevalence of IDA, it is still a major cause of anemia in young children.[5]

The last stage during iron depletion is a decrease in hemoglobin (Hb) concentration and the development of IDA.[1] There are several reasons that cause negative iron balance and consequent anemia, including impaired iron absorption, decreased iron absorption, insufficient iron intake, chronic blood loss.[6] Studies show that one-fifth of the world's population is iron deficient, and approximately 45% of children between the ages of 5 and 14 have anemia. Most of these children live in developing countries. About 56% of pregnant women in developing countries are also anemic.[7,8]

More important than anemia, however, are the long-term effects of neurobehavioral development and some irreversible effects.[4] Iron is one of the essential elements for many cellular functions.[9] Previous studies have shown an association between obesity and IDA in previous studies.[10]

The risks of anemia in children begin during pregnancy. Maternal anemia during pregnancy is associated with an increased risk of low birth weight and maternal and child mortality. Iron is needed to produce newborn red blood cells (RBCs) in the 1st months after birth.[11]

Breast milk is sufficient to supply infants' iron requirements up to 4–6 months of age. After 4 months to 24 months, the need for iron begins to increase.[12] Since iron stores are usually depleted around 6 months,[13] iron-fortified foods are recommended, which include meats, iron-containing products, and iron-fortified foods such as grains.[14] The current guidelines for iron supplements for children are based on the assumption that the iron in the body that is present at birth and in breast milk is sufficient for the first 6 months of life.[15]

Both WHO and United Nations International Children's Emergency Fund have recommended the use of iron supplements for prophylaxis or treatment of IDA in infants and toddlers. The WHO recommended that school children take 250 mg of folic acid and 30 mg of iron daily for 3 months to prevent ADA and ID.[16]

Oral iron supplements are the first line of supplementation for IDA.[17] The gold standard is ferrous sulfate (FS) oral iron therapy.[18] Other effective compounds include iron fumarate, gluconate, carbonyl iron, and iron-polysaccharide compounds. Considering the essential contribution of iron in the body and the high prevalence of ID in developing countries and as well as due to the necessity of prophylaxis of IDA in toddlers aging 6–24 months, the aim of this study was to compare the efficacy of daily supplementation with ferrous gluconate (FG) and FS on ferritin and Hb concentration to reduce the occurrence of IDA in toddlers.

Materials and Methods

Study design and setting

This study is a randomized, single-blind clinical trial; code IRCT20190902044674N1, which evaluated the effect of supplementation with FS or FG on prophylaxis of iron deficiency in toddlers 6–24 months old in the Amir-Kabir Hospital of Arak Province from March 2020 to December 2020.

Study participants and sampling

This study enrolled 129 toddlers aged 4–6 months old. Enrollment of participants and also allocation of intervention instructions was done by a pediatrician and researcher.

Randomization of patients in this study was stratified by factors known to influence hematologic parameters, including age, weight (at baseline), and exclusive breastfeeding to ensure the balance between treatment groups. Randomization was done using random number generation in Excel software; each patient has an identical number (ID) based on the visiting sequence and these IDs were entered in excel software. Thereafter, the "RAND" function was included in another column, the RAND function was entered for each patient where the random numbers were generated automatically in Excel rows. After applying the ascending sorting, the random numbers and the patient's IDs positions were changed randomly. The sorted IDs are divided into two groups; the first group is considered as FS treatment and the second as FG treatment categories. Eligible toddlers were randomized 1:1 to FS or FG equally to each group. The study was not blinded. All toddlers were healthy and had a similar and healthy diet. After obtaining informed consent and based on the type of iron supplement received, 120 healthy toddlers are categorized into 2 groups: FS group (n = 60), toddlers received 2 mg/kg/day FS supplementation, and FG group (n = 60), toddlers received 2 mg/kg/day FG supplementation. The weight of the toddlers was rechecked monthly and the dose of the supplements was adjusted based on the new weight.

Inclusion criteria included

Toddlers who progressed to iron deficiency (2 toddlers) and IDA with Hb < 9.5 g/dL (3 toddlers) at baseline (at the beginning of the study)[19] and who had chronic diseases, inflammatory or underlying diseases, and other hematologic disorders such as thalassemia and chronic diseases anemia were excluded from the study.

In addition, the toddlers had a diet other than breast milk (4 toddlers) were excluded from the study.

Flowchart of the participants through the trial was shown in Figure 1.

Data collection tool and technique

To measure hematologic parameters (Coulter Electronics, Ltd., UK), including Hb, hematocrit (Hct), RBCs, mean cell volume (MCV), mean corpuscular hemoglobin (MCH), MCH concentration (MCHC), red cell distribution width (RDW) and serum ferritin (Dade Behring, Inc., Newark, DE, USA), five ml of blood samples were collected in the EDTA tubes.

The samples were collected at baseline (at the beginning of the study) and after 6 months of supplementation. Healthy toddlers without anemia were randomly assigned to daily supplements with FS or FG chelate iron for 6 months. Mothers were advised to inject iron drops into the back of infants' mouths between feedings and then give them some water to prevent the darkening of the teeth.

Anemia was defined as Hb <11.0 g/dL.[20] ID was defined as ferritin level <10 mg/L or MCV <70 fL and RDW >14.5%.[21] Toddlers participating in the study were followed up every month in terms of prescribed supplements and possible side effects. The survey questionnaire was administered to the parents. To evaluate the side effects of supplements, a checklist was prepared and the toddlers' parents were asked to report side effects as yes or no. Adherence to treatment on children is performed by their parents. Parents were asked to report the following information if their infant received iron: name of supplement (FS or FG), age at the onset of supplementation, and age at the end of supplementation. Parental adherence to treatment was assessed in both groups receiving iron supplementation. Two questions were asked of this group of parents: (1) How and how many days a week did you give your infant iron? (2) Did you follow the instructions of the pediatrician? If the parents stated that their baby did not receive iron supplementation or that the parents' adherence to treatment was poor, they were openly asked about the reason for this.

After 6 months of supplementation, blood samples were taken from the toddlers again and their anthropometric and hematologic parameters were evaluated. Also, some side effects of iron supplementation, including anorexia, restlessness, diarrhea, vomiting, or constipation in toddlers, were evaluated.

Ethical considerations

Sampling began after obtaining a confirmation code from the Ethics Committee (ethical committee code number: IR.ARAKMU.REC.1398.016), obtaining a study permit from the officials of Amir-Kabir Hospital, Arak, Iran. The trial was registered at the Registry of Clinical Trials as IRCT20190902044674N1. The study was done according to the Declaration of Helsinki.[22] After expressing the aim of the study and the obtaining informed consent and based on the type of iron supplement received, toddlers were selected. Before starting the study, the parents of the eligible Toddlers were fully informed of the objectives of the study and were assured that the information would remain confidential.

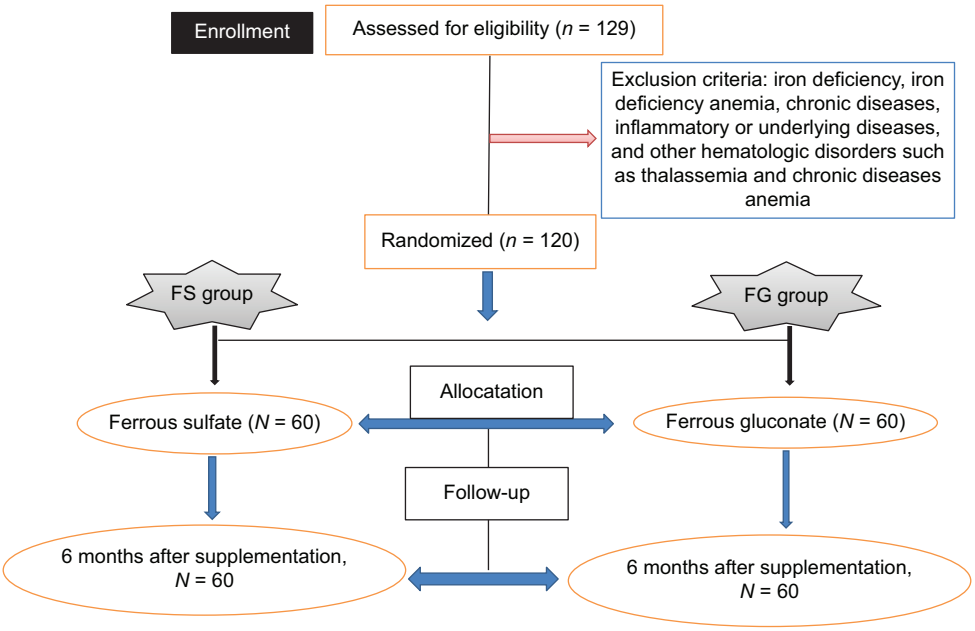

Figure 1: Flowchart of the study through the trial

Data analysis

The statistical significance of the differences in Hb, Hct, RBC, MCV, MCH, MCHC, RDW, and ferritin level between FS and FG groups was calculated using Student's *t*-test. Data are presented as mean ± standard deviation (SD). The two groups were compared using the Pearson's χ^2 test (or Fisher's exact test) for qualitative variables and the Student *t*-test for quantitative variables. SPSS software (version 16, Chicago, IL, USA) was used for statistical analysis. If the *P* value is 0.05 or lower, the result is considered significant.

The sample size was calculated using Pass 11 software with type I (a) error left at 5% and type II (b) error left at 20%, study power of 90% and based on the previous studies.[23,24] The mean ± SD was 11.2 ± 1.2 in FS group and 11.7 ± 1.1 in FG group. The sample size was determined in each group of 50 patients, but finally, considering the possibility of some patients becoming miss, the minimum sample size of 60 was considered.

Results

The mean ± SD age was 4.5 ± 2.1 months for the FS group and 4.7 ± 2.6 months for the FG group. A total of 120 toddlers, 61 females (50.8%) and 59 males (49.2%), were included in this study. During the course of the study, 9 toddlers dropped out and were excluded from the study (5 toddlers in FS group, 3 toddlers in FG group).

When groups were compared in terms of age and gender, no significant difference was observed between the groups ($P > 0.05$) [Table 1]. The groups were the same in terms of complementary foods and there was no difference between the groups.

At baseline (4–6 months of age), the mean ± SD Hb level of FS group and FG group were 10.52 ± 0.53 and 10.40 ± 0.46 g/dL, respectively, but after 6 months of prophylaxis, Hb level reached to 11.85 ± 0.83 and 12.11 ± 0.58 g/dL, respectively. At baseline, no significant difference was observed between groups in Hb level ($P = 0.656$) as well as other hematological parameters such as Hct ($P = 0.568$), RBCs count ($P = 0.632$), MCV ($P = 0.485$), MCH ($P = 0.540$), MCHC ($P = 0.521$), RDW ($P = 0.623$), and ferritin level ($P = 0.359$) [Table 2].

After 6 months of supplementation, no significant difference was observed in Hb level ($P = 0.245$), Hct ($P = 0.125$), RBCs count ($P = 0.230$), MCV ($P = 0.506$), MCH ($P = 0.356$), MCHC ($P = 0.132$), RDW ($P = 0.260$), and ferritin level ($P = 0.130$) between two groups [Table 2].

Comparison of hematological parameters of FS group toddlers before the start of prophylaxis (at baseline) and after 6 months of supplementation showed that there was a significant increase in Hb level ($P = 0.002$), Hct ($P = 0.004$), RBCs count ($P = 0.021$), and ferritin level ($P = 0.001$) [Table 2]. Comparison of hematological parameters of FG group toddlers before the start of prophylaxis (at baseline) and after 6 months of supplementation showed that there was a significant increase in Hb level ($P = 0.001$), Hct ($P = 0.004$), RBCs count ($P = 0.011$), and ferritin level ($P = 0.001$) [Table 2].

Comparison of hematological parameters between all toddlers before the start of prophylaxis (at baseline) and after 6 months of supplementation showed that there was a significant increase in Hb level ($P = 0.001$), Hct ($P = 0.004$), RBCs count ($P = 0.011$), and ferritin level ($P = 0.001$) [Table 2].

After 6 months of supplementation, a total of 49 toddlers were found to have ID and a total of 23 toddlers were found to have IDA. The number of toddlers with IDA was higher in the FS group than that of the FG group. No significant difference was observed between FS and FG groups with regard to the occurrence of ID and IDA after 6 months of supplementation ($P > 0.05$) [Table 3].

28 out of 60 toddlers (46.7%) in the FS group and 33 out of 60 toddlers (55%) in the FG group had no side effects from taking iron supplements [Table 4]. Overall, the most common side effects observed were constipation and vomiting. Thirty-two out of 60 toddlers (53.3%) in the FS group and 12 out of 60 toddlers (20%) in the FG group had one of the following side effects for one or more days. Six toddlers in the FS group (10%) and two toddlers in the FG group (3%) had more than one symptom. No statistically significant difference was observed between FS and FG groups in the occurrence of side effects ($P > 0.05$) [Table 4].

Table 1: Comparison of demographic and anthropometric findings between groups

	All toddlers (*n*=120)	FS group (*n*=60)	FG group (*n*=60)	*P*
Male, *n* (%)	59 (49.2)	31 (51.7)	28 (46.7)	0.836
Female, *n* (%)	61 (50.8)	29 (48.3)	32 (53.3)	
Weight, at birth	3.2±0.1	3.1±0.5	3.1±0.3	0.428
Weight, at baseline	6.±1.1	6.6±1.3	6.4±1.0	0.697
Weight, after 6 months of supplementation	9.9±1.1	9.7±1.2	10.0±1.1	0.367

FS=Ferrous sulfate, FG=Ferrous gluconate

Table 2: Hematologic parameters of groups at baseline and after 6 months of supplementation

Variables/iron supplements	Baseline (*n*=120)				Supplementation (*n*=120)				*P**	*P***	*P****
	FS (*n*=60)	FG (*n*=60)	All (*n*=120)	*P*	FS (*n*=60)	FG (*n*=60)	All (*n*=120)	*P*			
Hb level (g/dL)	10.52±0.53	10.40±0.46	10.46±0.49	0.656	11.85±0.83	12.11±0.58	12.45±0.01	0.245	0.002	0.001	0.001
Hct (%)	32.38±1.32	33.46±1.28	32.40±1.30	0.568	35.58±2.33	36.38±1.86	35.98±1.02	0.125	0.004	0.004	0.004
RBCs count, ($\times10^{12}$/L)	3.94±0.25	3.97±0.24	3.95±0.24	0.632	4.21±0.41	4.35±4.77	4.28±1.10	0.230	0.021	0.011	0.011
MCV (fL)	74.63±1.69	75.06±1.47	74.85±1.59	0.485	74.65±2.41	75.80±2.13	75.22±1.3	0.506	0.511	0.634	0.558
MCH (pg)	27.5±0.67	27.66±0.72	27.60±0.70	0.540	27.36±1.30	27.93±1.05	27.64±1.21	0.356	0.498	0.761	0.597
MCHC (g/dL)	30.68±0.89	30.71±0.88	30.70±0.88	0.521	30.56±1.06	31.06±1.02	30.81±0.12	0.132	0.821	0.735	0.710
RDW (%)	14.12±1.31	14.24±1.20	14.18±1.25	0.623	14.91±2.39	14.48±1.78	14.69±1.04	0.260	0.357	0.472	0.399
Ferritin level (µg/L)	28.18±4.91	27.98±6.04	28.08±5.48	0.359	58.25±10.24	61.00±9.50	59.63±3.54	0.130	0.001	0.001	0.001

**P* Comparison of hematologic parameters of FS group at baseline and after 6 months of supplementation, ***P* Comparison of hematologic parameters of FG group at baseline and after 6 months of supplementation, ****P* Comparison of hematologic parameters between all toddlers at baseline and after 6 months of supplementation, Data are presented as mean±SD. FS=Ferrous sulfate, FG=Ferrous gluconate, SD=Standard of deviation, Hb=Hemoglobin, Hct=Hematocrit, RBCs=Red blood cells, MCV=Mean cell volume, MCH=Mean corpuscular hemoglobin, MCHC=MCH concentration, RDW=Red cell distribution width

Table 3: Comparison between ferrous sulfate group and ferrous gluconate group with regard to the occurrence of iron deficiency and iron-deficiency anemia after 6 months of supplementation by definition

Definition	FS group		FG group		*P**	*P***
	ID (*n*=28), *n* (%)	IDA (*n*=13), *n* (%)	ID (*n*=21), *n* (%)	IDA (*n*=10), *n* (%)		
Ferritin alone	13 (21.6)	7 (11.6)	11 (18.3)	5 (8.3)	0.194	0.487
MCV and RDW	10 (16)	4 (6.6)	7 (11.6)	3 (5)		
MCV and RDW and ferritin	5 (8.3)	2 (3.3)	3 (5)	2 (3.3)		

**P* Comparison of ID in FS group and FG group, ***P* Comparison of IDA in FS group and FG group. MCV=Mean corpuscular volume, RDW=Red cell distribution width, ID=Iron deficiency, IDA=Iron-deficiency anemia, FS=Ferrous sulfate, FG=Ferrous gluconate

Table 4: Side effects after received iron supplements

Side effects	All (*n*=120), *n* (%)	FS group† (*n*=60), *n* (%)	FG group‡ (*n*=60), *n* (%)	*P*
Anorexia	4 (3.3)	0	4 (6.7)	0.119
Restlessness	5 (4.2)	3 (5)	2 (3.3)	0.999
Diarrhea	4 (3.3)	0	4 (6.7)	0.119
Constipation	16 (13.3)	14 (23.3)	8 (13.3)	0.238
Vomiting	15 (12.5)	15 (25)	9 (15)	0.254
Toddlers with anysymptom	52 (43.3)	26 (43.3)	10 (16.7)	0.003
None	76 (63.3)	28 (46.7)	33 (55)	0.465

†Six toddlers had more than one symptom but they were counted only once, ‡Two toddlers had more than one symptom but they were counted only once. FS=Ferrous sulfate, FG=Ferrous gluconate

Discussion

In our study, both FS and FG prophylaxis groups showed a significant improvement in their hematological parameters after 6 months of supplementation. Therefore, FS and FG supplements can be effective in the prophylaxis of ID and IDA in toddlers. However, FG was more effective than FS because FG group that received FG supplementation indicated a higher Hb and ferritin levels in comparison to the FS group that received FS supplementation. However, we should note the increase in physiological Hb levels from 4 months to 12 months during the 1st year of life.[25]

In parallel with our study, in a study about the efficacy and safety of IDA prophylaxis with FG and Iron Polymaltose Complex (IPC) in healthy infants after a fortification intervention, the authors found supplementing with FG and IPC for 6 months, prevent IDA in infants and IPC and FG are both suitable iron supplements.[23] In a study about the effect of supplementation with FS and iron bis-glycinate chelate on ferritin concentration in schoolchildren with iron deficiency in Mexican by schoolchildren without anemia after a fortification intervention, the authors found supplementing with FS or iron bis-glycinate chelate for 3 months had a positive effect on increasing ferritin level in schoolchildren with low iron stores, and this effect persisted after 6 months of supplementation[26] which was consistent with our findings.

The results of our study are valuable as little information is available on ID prophylaxis in toddlers. Studies in adults on iron deficiency prophylaxis have also yielded conflicting results.[27] Yalçın *et al*. reported that treatment with iron supplements is an appropriate and effective strategy to prevent IDA in toddlers at 4–6 months of age.[28] They also suggested that the type of iron supplementation used to prevent did not have significant efficiency in the occurrence of anemia which

was consistent with the results of this study. Dos Santos *et al*. confirmed the effectiveness of the iron supplements including iron salts and ferrous bis-glycinate chelate every week to overcome iron deficiency and IDA.[29] Hurrell reported that infants and young children with iron deficiency absorb less ferrous fumarate supplement than FS supplement.[30] Ortiz *et al*. administered oral IPC and FS to pregnant women with IDA and demonstrated favorable efficacy in the treatment of IDA during the course of the pregnancy, with a significant increase in Hb, after 3 months of supplementation.[31]

In this study, the occurrence of IDA was found to be 21.6% in the FS group and 16.6% in the FG group, with a total occurrence of 19.1%. In the study of Aydin *et al*.,[32] overall occurrence of IDA was found to be 15.1%; in the study of Jaber *et al*.,[23] overall occurrence of IDA was found to be 12.4%, and in the study of Yalçın *et al*.,[28] overall occurrence of IDA was found to be 7.3%, which were lower than the occurrence found in our study. One of the reasons for the difference in results may be the difference in sampling time and the duration of the prophylaxis period. The sampling time to assess IDA in the studies of Aydin *et al*.,[32] Jaber *et al*.,[23] and Yalçın *et al*.[28] were 9, 12, and 12–23 months, respectively. Yalçın *et al.* reported that younger infants were at higher risk for iron deficiency.[28] Furthermore, in another study about the effect of prophylaxis with 1 mg/kg daily iron (Fe) in infants 4 months of age, the authors reported that the occurrence of IDA was 26% at 7 months of age and after 3 months of iron supplementation[33] which was higher than the occurrence found in our study. Therefore, according to the results of this study and other studies, we suggest that the age of infants at the time of sampling to assess IDA and the determined dose of iron supplements play an important role in the occurrence of IDA.

The results of this study, as well as other studies, suggested that the use of iron supplements or nutrition with iron-fortified foods can lead to prophylaxis of ID and IDA.[3] Although the use of daily iron supplements is highly recommended for the prophylaxis and treatment of IDA, information on the best and most effective iron supplements is scarce and the efficacy and safety of iron supplementation programs is controversial.[3,34]

This study showed that the side effects of FG were less than FS. Therefore, FG can be used in cases where FS had undesirable side effects. This may be one of the reasons why the toddlers and/or their parents dropped out of the study. In parallel with our study, Jaber *et al*. reported that adverse effects such as vomiting, diarrhea, and constipation were significantly less common in the FG than IPC.[23] Furthermore, in another study, Aydin *et al*. reported that gastrointestinal disorders such as diarrhea, constipation, and vomiting were the most common side effects without any significant difference between the groups (FS vs. ferric polymaltose). However, diarrhea and vomiting were higher in FS prophylaxis group than in ferric polymaltose group although statistically insignificant difference.

Limitation and recommendation

One of the limitations of this study was since some toddlers may already have anemia, previous diagnosis and treatment of anemia that may have affected the results. Another limitation of this study is that mothers suffer from IDA during childbirth and breastfeeding. It is recommended to evaluate these findings in larger epidemiological studies. One of the benefits of this study is that it does not cause IDA and AD in case of iron prophylaxis and its inclusion in the diet of toddlers.

Conclusions

Although prophylaxis with FG led to a higher Hb and ferritin levels, our study recommended that both FG and FS supplements were effective for prophylactic use in the prevention of ID and IDA with different side effects. It is recommended that at the time of prescribing the iron supplements for prophylaxis or treatment of ID and IDA, issues such as tolerance, side effects, determine the exact dose of the iron supplements through regular monitoring of the infant's weight, duration of the prophylaxis period and effectiveness of iron supplements should be considered.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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